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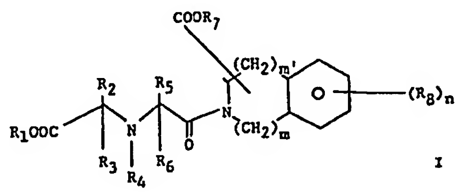
(54) N-(substituted aminoalkanoyl)heterocyclic compounds

(57) Compounds of the formula



I

wherein

R_1 and R_7 are hydrogen, lower alkyl or phenyl lower alkyl,

R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, fused aryl-cycloalkyl, aralkyl, cycloalkyl, heterocyclic, substituted lower alkyl, lower alkenyl, and lower alkynyl groups wherein the substituent is hydroxy, alkoxy, halo, amino, alkylamino, mercapto and alkylmercapto groups, and substituted cycloalkyl, aryl and heterocyclic groups in which the substituent is alkyl, hydroxy, alkoxy, hydroxyalkyl, halo, mercapto, alkylmercapto, mercaptoalkyl, haloalkyl, amino, alkylamino, aminoalkyl, nitro, methylenedioxy, and trifluoromethyl;

each R_8 is lower alkyl, lower alkenyl, lower alkynyl, nitro, amino, alkylamino, dialkylamino, hydroxy, alkoxy, mercapto, alkylmercapto, hydroxyalkyl, mercaptoalkyl, halogen, haloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonamido, methylenedioxy, or trifluoromethyl,

m is an integer from 0 to 2 inclusive;

m' is an integer from 1 to 3 inclusive, provided that when m is 0, m' is 2 or 3 and, when m is other than 0, m' is 1 or 2;

n is an integer from 0 to 4 inclusive, and salts thereof, especially pharmaceutically acceptable salts with an acid or a base.

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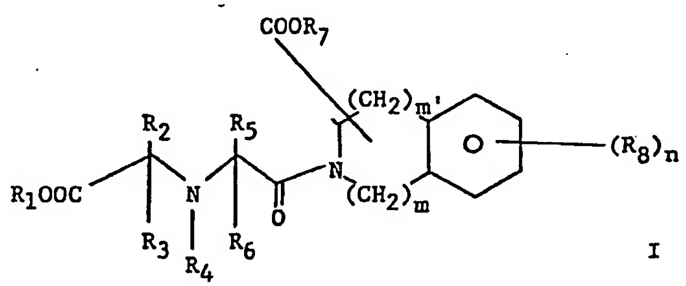
SPECIFICATION
Amido-amino acids

This invention relates to new compounds having valuable pharmacological activity. It particularly relates to compounds having antihypertensive and angiotensin converting enzyme inhibitory activity and the structure



I

wherein

R_1 and R_7 are each hydrogen, lower alkyl, or phenyl lower alkyl; R_2, R_3, R_4, R_5 and R_6 are each hydrogen, alkyl, alkenyl, alkynyl, aryl, fused aryl-cycloalkyl, aralkyl, cycloalkyl, and heterocyclic, and may be the same or different;

each R_8 is alkyl, alkenyl, alkynyl, nitro, amino, alkylamino, dialkylamino, hydroxy, alkoxy, mercapto, alkylmercapto, hydroxyalkyl, mercaptoalkyl, halogen, haloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonamido, methylenedioxy, and trifluoromethyl, and where there is more than one R_8 group, the groups may be the same or different;

m is an integer from 0 to 2; and m' is an integer from 1 to 3 provided that when m is 0, m' is 2 or 3 and when m is other than 0, m' is 1 or 2;

n is an integer from 0 to 4;

and salts thereof especially salts with pharmaceutically acceptable acids and bases.

The alkyl groups in alkyl *per se*, aralkyl, alkoxy, aminoalkyl, thioalkyl, haloalkyl, and hydroxyalkyl are preferably lower alkyl containing 1 to 6 carbon atoms and may be branched or straight chain.

The alkenyl and alkynyl groups contain from 2 to 6 carbon atoms and may be branched or straight chain.

The alkyl, alkenyl, and alkynyl groups may carry substitutents such as hydroxy, alkoxy, halo, amino, alkylamino, mercapto and alkylmercapto.

The cycloalkyl groups contain from 3 to 7 carbon atoms. Such cycloalkyl groups include cycloalkyl-alkyl and the cycloalkyl groups may carry substituents such as alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, amino, aminoalkyl, alkylamino, trifluoromethyl, and nitro.

The aryl groups may have from 6 to 10 carbons and include phenyl and α- and β-naphthyl. The aryl groups may contain substituents such as alkyl, hydroxy, alkoxy, hydroxyalkyl, mercapto, alkylmercapto, mercaptoalkyl, halo, haloalkyl, amino, alkylamino, aminoalkyl, nitro, methylenedioxy, trifluoromethyl, ureido and guanidino.

The fused aryl-cycloalkyl comprise phenyl rings fused to cycloalkyl rings having from 3 to 7 carbon atoms. These groups also include fused aryl-cycloalkyl-alkyl.

The heterocyclic group may be saturated, partially saturated or unsaturated and includes such groups as pyridine, piperidine, morpholine, pyrrole, pyrrolidine, thiomorpholine, quinoline, isoquinoline, tetrahydroquinoline, thiazolidine, thiazoline, thiazole, imidazolidine, imidazoline, imidazole, thiophene, tetrahydrothiophene, furyl, tetrahydrofuran, and the like. These heterocyclic groups may also carry substituents as described for the aryl groups above. The heterocyclic group also includes heterocyclic lower alkyl.

The halo groups include fluorine, chlorine, bromine and iodine.

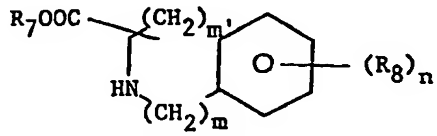
Preferably, the —$COOR_7$ group is attached to a carbon adjacent to the nitrogen of the ring system.

Suitable acid addition salts include inorganic salts such as hydrochloride, phosphate and sulfate; organic carboxylates such as acetate, malate, maleate, furmarate, succinate, citrate, lactate, benzoate, hydroxybenzoate, aminobenzoate, nicotinate, and the like, and organic sulfonic and phosphonic acids such as toluenesulfonic acid.

Suitable basic salts include alkali and alkaline earth metal salts such lithium, sodium, potassium, magnesium and calcium and iron, as well as ammonium and quarternary ammonium salts.

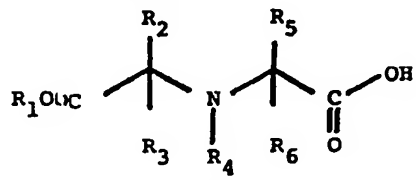
It is to be understood that the compounds of the present invention may have one or more asymmetric carbon atoms and the various racemic mixtures as well as the individual optically active compounds are considered to be within the scope of the present invention.

The compounds of the present invention may be prepared by amide forming reaction of an amine compound of the formula



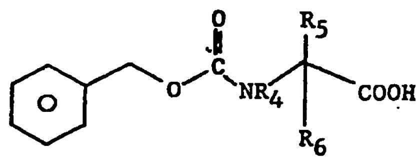
II

with an acylating derivative of the acid of the formula:



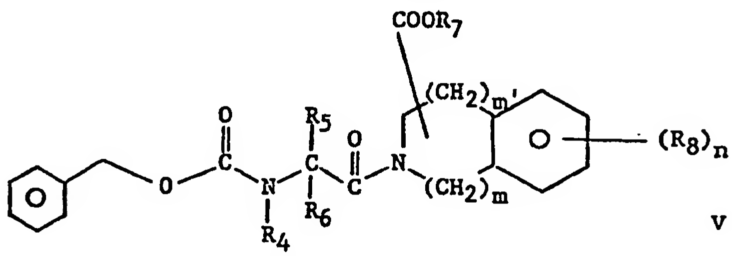
III

Alternatively, the compounds in which R_3 and R_4 are hydrogen may be readily prepared by treating a compound of formula II with a compound of the formula



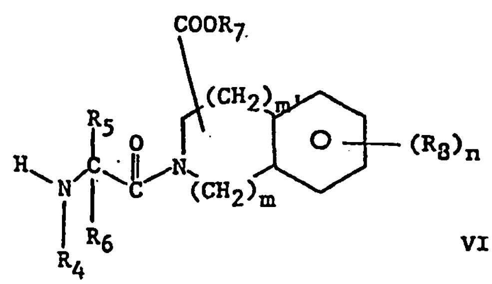
IV

under amide-forming conditions to form a compound of the structure



V

splitting off the carbobenzyloxy group to give a free amine of the structure



VI

and reacting the amine with an α-keto acid or ester of the formula

$$R_1OOC{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R_2 \qquad \text{VII}$$

and reducing the resulting imine to give a compound of formula I wherein R_3 and R_4 are hydrogen.

Compounds of formula VI can also be reacted with an α-halo acid or ester of the formula

$$R_1OOC{-}\overset{\displaystyle R_2}{\underset{\displaystyle R_3}{\overset{|}{\underset{|}{C}}}}{-}Hal \qquad \text{VIII}$$

to give compounds of formula I wherein R_3 and R_4 can be H or any of the other substituents descriptive of the said R_3 and R_4.

In the above sequence of reactions R_1 to R_8, m, m′ and n are as hereinbefore defined and Hal is halogen.

Preferably, R_1, R_3, R_4, R_5 and R_7 and R_8 are hydrogen. R_2 is lower alkyl or phenyl-lower alkyl, R_6 is lower alkyl.

The amide forming conditions referred to herein involve the use of known derivatives of the described acids, such as the acyl halides, anhydrides, mixed anhydrides, lower alkyl esters, carbodiimides, carbonyl diimidazoles, and the like. The reactions are carried out in organic solvents such as acetonitrile, tetrahydrofuran, dioxane, acetic acid, methylene chloride, ethylene chloride and similar such solvents. The amide forming reaction will occur at room temperature or at elevated temperature. The use of elevated temperature is for convenience in that it permits somewhat shortened reaction periods. Temperatures ranging from 0°C up to the reflux temperature of the reaction system can be used. As a further convenience the amide forming reaction can be effected in the presence of a base such as tertiary organic amines, e.g., trimethylamine, pyridine, picolines and the like, particularly where hydrogen halide is formed by the amide-forming reaction, e.g., acyl halide and amino compound. Of course, in those reactions where hydrogen halide is produced, any of the commonly used hydrogen halide acceptors can also be used.

In the condensation of an alpha haloacid derivative of formula VIII herein, similar reaction conditions, solvents and hydrogen halide acceptors can be used as for amide formation.

Various substituents on the present new compounds, e.g., as defined for R_8, can be present in the starting compounds or added after formation of the amide products by the known methods of substitution or conversion reactions. Thus, the nitro group can be added to the final product by nitration of the aromatic ring and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Other reactions can be effected on the formed amide product. Amino groups can be alkylated to form mono and dialkylamino groups, mercapto and hydroxy groups can be alkylated to form corresponding ethers. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the final products. Of course, reactive groups where present should be protected by suitable blocking groups during any of the aforesaid reactions particularly the condensation reactions to form the amide linkages.

The acid and base salts of the present new compounds can be formed using standard procedures. Often, they are formed *in situ* during the preparation of the present new amido amino acids.

The present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers, which can be resolved. Alternatively, by selection of specific isomers as starting compounds, the preferred stereoisomer can be produced. Therefore, the preferred forms, where each asymmetric center (chairal center) is S-configuration, are preferably prepared by the stereospecific route rather than attempting resolution of mixtures of isomers. The compounds in which the S-configuration exists at all asymmetric centers are the most active; those in which the R-configuration exists are of less activity; and those where both R- and S-configurations exist are of intermediate activity.

The invention is further illustrated by the following examples.

Example 1

A. 2-(N-benzyloxycarbonyl-L-alanyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester

To a suspension of 10.0 g (43.9 mmols) of L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester hydrochloride and 10.4 g (46.6 mmols) of carbobenzyloxy-L-aniline in 150 ml dry acetonitrile was added 4.4 g (43.6 mmols) of triethylamine. A solution of 9.2 g (44.6 mmol) of N,N-dicyclohexylcarbodiimide in 5 ml dry acetonitrile was then added dropwise with stirring. The resulting slurry was stirred overnight at room temperature, filtered and concentrated *in vacuo*. The residue was redissolved in ether, washed successively with 1N HCl, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to give 18.3 g (105%) of crude amide which was used without further purification.

B. 2-(N-benzyloxycarbonyl-L-alanyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

8.0 g of the crude amide ester from A was dissolved in 25 ml 1N NaOH/MeOH. To this was added 5 ml water. The resulting solution was stirred overnight at room temperature, then poured into 150 ml water and extracted with ether. The aqueous layer was then acidified and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated at aspirator pressure to give 5.5 g of product. After prolonged concentration at oil pump vacuum there was obtained a brittle foam.

C. 2-L-alanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrobromide

To a solution of 4.8 (12.5 mmol) crude carbobenzyloxycarboxylic acid in 7 ml acetic acid was added 5 ml of saturated HBr in acetic acid. The solution was stirred at room temperature until all gas evolution had ceased (1—1.5 hr). A slow stream of air was passed through the solution to remove excess HBr, then 25 ml ether was added to precipitate the product. The solid was washed with two further portions of ether, then dried *in vacuo* to give 2.2 g of pale yellow solid, m.p. 180°.

D. N-(1-carboxy-3-phenylpropyl)alanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

To a solution of 1.3 g (6.63 mmol) of benzylpyruvic acid hydrate in 5 ml. sat. $NaHCO_3$ was added 0.307 g (0.93 mmol) of alanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, followed by 0.238 g (3.79 mmol) of sodium cyanoborohydride. The solution was stirred overnight at room temperature then transferred to a column holding 20 g of Dowex 50X8 ("Dowex" is a registered Trade Mark). The column was eluted with 50% MeOH, then 3% NH_4OH. The first ammonia fractions, containing the desired product, were combined and lyophilized to give 85 mg of product as a fluffy white powder, m 97—101°.

Example 2

A. 2-(N-carbobenzyloxy-L-valyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester.

To a suspension of 4.4 g (19.3 mmols) of L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester hydrochloride in 50 ml dry acetonitrile were added 5.2 g (20.7 mmols) N-carbobenzyloxy-L-valine, 2.7 g (20.0 mmols) 1-hydroxybenzotriazole and 2.1 g (20.7 mmols) triethylamine. The resulting mixture was stirred at room temperature and a solution of 4.5 g (21.8 mmols) of dicyclohexylcarbodiimide in 10 ml dry acetonitrile was added slowly. The mixture was stirred overnight at room temperature, then filtered and worked up as described in Example 1A. Final concentration gave 8.3 g (101%) of a thick oil.

B. 2-(N-carbobenzyloxy-L-valyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

4.5 g (106 mmols) of crude methyl ester prepared according to the above procedure was treated with 10 ml 10% NaOH and sufficient methanol (35—40 ml) to produce a homogeneous solution. This solution was stirred at room temperature for 23 hrs., then diluted with 100 ml water and extracted with two 25 ml portions ether. The aqueous fraction was then acidified and extracted with four 10 ml portions methylene chloride. The extracts were dried over $MgSO_4$ and concentrated to give 3.8 g (9.3 mmols, 87%) of homogeneous carboxylic acid.

Example 3

A. 2-(N-carbobenzyloxy-L-isoleucyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

4.5 g (19.8 mmols) of L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester hydrochloride, 5.3 g (20.0 mmols) of N-carbobenzyloxy-L-isoleucine, 2.7 g (20.0 mmols) 1-hydroxybentriazole, and 2.1 g (20.7 mmols) triethylamine were treated as described for example 2A with 4.4 g (21.3 mmols) dicyclohexylcarbodiimide, then worked up to give 7.8 g (90%) of crude methyl ester. This was dissolved in 30 ml methanol and treated with 10 ml 10% NaOH. The solution was stirred overnight at room temperature, then worked up as previously described to give 1.8 g (21.4% overall) of the desired acid as a yellow oil.

Example 4

2-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-isoquinaldic acid

An ethanolic solution of benzyl 2-(N-carbobenzyloxy-L-alanyl)-isoquinaldate was hydrogenated with palladium on carbon. The solution was filtered and treated with ethyl 2-oxo-4-phenyl-butyric acid, alkali and sodium cyanoborohydride as in Example 1D. The product is purified by chromatography and lyophilization.

Example 5

2-N-(1-carboxyethyl)-L-alanyl-isoquinaldic acid

An ethanolic solution of benzyl 2-(N-carbobenzoxy)-L-alanyl)-isoquinaldate and pyruvic acid was hydrogenated with palladium on carbon. The filtered solution was concentrated and purified as in Example 1D.

Example 6

A. 1-(N-carbobenzoxy-L-alanyl)-2-benzoxycarbonylindoline

A methylene chloride solution of N-carbobenzyloxy-L-alanine and 2-benzyloxycarbonyl-indoline was treated with N,N′-dicyclohexylcarbodiimide. Purification of the product ws accomplished by chromatography on silica gel.

B. 1-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2-carboxy-indoline

An ethanolic solution of 1-(N-carbobenzyloxy-L-alanyl)-2-benzyloxycarbonyl-indoline was hydrogenated with palladium on carbon. To the filtered solution was added ethyl 2-oxo-4-phenylbutyric acid, alkali and sodium cyanoborohydride as in Example 1D. The product was purified by chromatography and lyophilization.

Example 7

1-[N-(1-carboxyethyl)-L-alanyl]-2-carboxy-indoline

An ethanolic solution of 1-(N-carbobenzyloxy-L-alanyl)-2-benzyloxycarbonyl-indoline was hydrogenated with palladium on carbon. To the filtered solution was added ethyl pyruvate, alkali and sodium cyanoborohydride. The product was purified by chromatography and lyophilization.

Example 8

1-Benzyloxycarbonyl-2-(N-carbobenzyloxy-L-alanine)-5H-1,2,3,4-tetrahydro-2-benzazepine

A methylene chloride solution of N-carbobenzyloxy-L-alanine and 1-benzyloxycarbonyl-5H-1,2,3,4-tetrahydro-2-benzazepine was treated with N,N'-dicyclohexylcarbodiimide as in Example 3A. Purification of the final product was accomplished by silica gel chromatography.

Example 9

1-Carboxy-2-N-(1-carboxy-3-phenylpropyl)-L-alanyl-5H-1,2,3,4-tetrahydro-2-benzazepine

An ethanolic solution of 1-benzyloxycarbonyl-2-(N-carbobenzyloxy-L-alanyl)-5H-1,2,3,4-tetrahydro-2-benzazepine was hydrogenated with palladium on carbon. The filtered solution was treated with alkali, sodium cyanoborohydride and 2-oxo-4-phenylbutyric acid as in Example 1D. The product was purified by chromatography.

Example 10

1-Carboxy-2-[N-(1-carboxy-3-methylbutyl)-L-alanyl]-5H-1,2,3,4-tetrahydro-2-benzazepine

An ethanolic solution of 1-benzyloxycarbonyl-2-(n-carbobenzyloxy-alanyl)-5H-1,2,3,4-tetrahydro-2-benzazepine was hydrogenated with palladium on carbon. The filtered solution was treated with 2-oxo-4-methylpentanoic acid, sodium cyanoborohydride and alkali as in Example 1D. Chromatography and lyophilization provided the pure product.

Example 11

2-(N-(1-carboethoxy-3-phenylpropyl)-L-alanyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

By the procedure in Example 1A 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester was coupled with carbobenzyloxy-L-alanine using dicyclohexylcarbodiimide in acetonitrile. The crude neutral product was then hydrolyzed with two equivalents of NaOH in 80% MeOH to give the desired carboxylic acid.

The above carbobenzyloxy-dipeptide was deprotected according to the procedure in Example 1C with an initial reaction temperature of 0°C. 0.675 g (1.81 mmol) of this dipeptide was added to a solution of 1.47 g (7.13 mmol) of ethyl 2-oxo-4-phenylbutyrate in 25 ml EtOH. The pH was adjusted to 6.80 with ethanolic NaOH and 0.35 g (5.57 mmol) of sodium cyanoborohydride was added. After stirring for 24 hours at room temperature a further 0.70 g of ester and 0.2 g of $NaBH_3CN$ were added and the stirring continued an additional 48 hours. The reaction mixture was transferred to a column of Dowex 50X8 and the column eluted with 50% EtOH, H_2O, 1% NH_4OH, and 3% NH_4OH. Fractions containing the desired product were combined and lyophilized to give 0.347 g of the diastereomeric mixture.

Example 12

2-(N-(1-carboethoxy-1-(2-indanyl)methyl)-L-alanyl)-6-chloro-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

In a similar manner the appropriate dipeptide was prepared from 6-chloro-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester and carbobenzyloxy-L-alanine by DCC coupling followed by saponification and cleavage with HBr/HOAc.

The above dipeptide (0.427 g, 1.17 mmol) was alkylated as described above by 1.5 g (6.87 mmol) of ethyl α-oxindane-2-acetate and 0.32 g (5.09 mmol) of $NaBH_3CN$ at pH 6.75. After 24 hours a second 0.85 portion of the keto ester and 0.2 g $NaBH_3CN$ were added. The reaction was then stirred for 40 hours. Ion exchange chromatography then gave 0.183 g of desired product.

Example 13

2-(N-(1-carboethoxy-3-(2-pyridyl)propyl)L-valyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

The starting dipeptide was prepared as indicated above from 6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester and carbobenzyloxy-L-valine.

Hydroxybenzotriazole-mediated DCC coupling, followed by saponification and deblocking as before, gave the dipeptide salt. Reductive alkylation with ethyl 2-oxo-4-(2-pyridyl)butyrate in the presence of sodium cyanoborohydride under standard conditions gave the crude monoester. This was purified by ion exchange chromatography and lyophilization as before to give a mixture of diastereomers of the desired product.

Example 14

2-(N-(1-carboethoxy-3-(4-methoxyphenyl)propyl)-L-isoleucyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

The starting dipeptide was prepared from carbobenzyloxy-L-isoleucine and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester using hydroxybenzotriazole and DCC as previously described. Saponfication and deprotection as before then gave the dipeptide hydrobromide.

Treatment with ethyl 2-oxo-4-(4-methoxyphenyl)butyrate and sodium cyanoborohydride under the above standard conditions gave the reductive alkylation product. This was purified as before to give the title compound as a diastereomeric mixture.

Example 15

2-(N-(1-carboethoxy-3-(4-chlorophenyl)-L-alanyl)-7-methoxy-1,2,3,4-tetrahydro-5H-benz[c]azepine-3-carboxylic acid

Acylation of 1,2,3,4-tetrahydro-5H-benz[c]azepine-3-carboxylic acid methyl ester with carbobenzyloxy-L-alanine using DCC as coupling reagent as in Example 1A gave the protected dipeptide. Saponification and deblocking then gave the free dipeptide as previously described.

N-alkylation with ethyl 2-oxo-4-(4-chlorophenyl)butyrate and sodium cyanoborohydride as in Example 12 gave a mixture containing the desired product. This was isolated by ion exchange chromatography and lyophilization as previously described.

Example 16

2-(N-(1-carboethoxy-3-(4-pyridyl)propyl)-L-alanyl)-1,2,3,4-tetrahydro-5H-benz[c]azepine-3-carboxylic acid

The starting dipeptide was prepared from carbobenzyloxy-L-alanine and 1,2,3,4-tetrahydro-5H-benz[c]azepine-3-carboxylic acid methyl ester according to the general procedure of Example 1. Reductive alkylation as described previously, using ethyl 2-oxo-4-(4-pyridyl)butyrate and sodium cyanoborohydride, gave crude N-alkylated peptide. Purification by ion exchange chromatography and lyophilization gave the pure title compound as a mixture of diastereomers.

Example 17

2-(N-1-(carboethoxy-3-(3-trifluoromethylphenyl)propyl-L-valyl)-7,8-methylendioxy-1,2,3,4-tetrahydro-5H-benz[c]acepine-3-carboxylic acid

Acylation of 7,8-methylenedioxy-1,2,3,4-tetrahydro-5H-benz[c]azepine-3-carboxylic acid methyl ester with carbobenzyloxy-L-valine using hydroxybenzotriazole and DCC according to Example 2A gave the protected dipeptide. This was sequentially saponified and treated with HBr/HOAc to give the desired peptide.

Treatment of the dipeptide with ethyl 2-oxo-4-(3-trifluoromethylphenyl)butyrate and sodium cyanoborohydride at pH 6.55 according to Example 12 gave the N-alkylated product. Ion exchange chromatography and lyophilization gave the pure compound as a mixture of diastereomers.

Example 18

Stereospecific synthesis of the S-configuration compounds is accomplished by the following procedure.

A. 2-(N-(1-carboethoxy-3-phenylpropyl)alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid benzyl ester

To a suspension of 2.60 g (9.31 mmol) of (S,S)-N-(1-carboethoxy-3-phenylpropyl)alanine in 20 ml dry THF was added 1.51 g (9.3 mmol) of 1,1′-carbonyldimidazole. When a clear solution was obtained (5—10 min.), the reaction mixture was cooled to 0° and 3.12 g (7.44 mmol) of (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid benzyl ester monotartrate was added. The reaction mixture was allowed to stir at room temperature overnight, then concentrated *in vacuo* and redissolved in ether. The ether solution was washed with saturated $NaHCO_3$ solution and water and concentrated to give 2.2 g (56%) of the desired amide, which was used without further purification

CIMS: 529 (n=1), 234, 91
NMR: 7.3, 5.1, 3.15, 2.8, 1.2—1.5

B. 2-(N-(1-carboethoxy-3-phenylpropyl)alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride

To a solution of 2.10 g (3.97 mmol) of (S,S,S)-2-(N-(1-carboethoxy-3-phenylpropyl)alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid benzyl ester in 20 ml ethanol was added 0.2 g 10% Pd/C catalyst. The mixture was shaken under *ca.* 2 atm. hydrogen until uptake ceased. The reaction mixture was filtered and concentrated *in vacuo*, then partitioned between ether and 2N HCl. The aqueous solution was lyophilized and the resulting powder washed with ether to give 0.70 g (37%) of product, m. 101—105°.

$[\alpha]_d$ −10.9° (H_2O)
CIMS 421 (M+1—H_2O)
EIMS 421, 316, 270

Calc. for $C_{25}H_{31}N_2O_5 \cdot HCl \cdot H_2O$		C 60.91 H 6.74 N 5.18
	Found	C 61.16 H 6.47 N 5.48

Following the procedures of the above examples, the following additional compounds were prepared:

2-[N-1-Ethoxycarbonyl-3-methylbutyl)-L-alanyl]-isoquinaldic acid
2-[N-1-Ethoxycarbonyl-4-methylhexyl)-L-alanyl]-isoquinaldic acid
2-[N-1-Ethoxycarbonyl-5-methylhexyl)-L-alanyl]-isoquinaldic acid
2-[N-1,3-Dicarboxypropyl)-L-alanyl]-isoquinaldic acid
2-[N-1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-6-hydroxyisoquinaldic acid
2-[N-1-Ethoxycarbonyl-5-methylhexyl)-L-valyl]-isoquinaldic acid
2-[N-1,3-Dicarboxypropyl)-L-alanyl]-6-methoxy-isoquinaldic acid
2-[N-1-Ethoxycarbonylhexyl-L-valyl]-8-methyl-isoquinaldic acid
2-[N-1-Ethoxycarbonyl-3-phenylpropyl)-L-phenylalanyl]-6-chloroisoquinaldic acid
2-[N-1-Ethoxycarbonyl-3-phenylpropyl)-L-histidyl]-8-hydroxyisoquinaldic acid
1-[N-(1-Ethoxycarbonyl-3-methylbutyl)-L-alanyl]-2-carboxyindoline
1-[N-(1-Ethoxycarbonyl-3-phenylpropyl)-L-phenylalanyl]-2-carboxy-indoline
1-[N-(1-Ethoxycarbonylhexyl)-L-alanyl]-2-carboxyindoline
1-[N-(1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl]-2-carboxy-5,6-dimethylindoline
1-[N-(1-Ethoxycarbonyl-3-phenylpropyl)-L-valyl]-2-carboxyindoline
1-[N-(1,3-Dicarboxypropyl)-L-alanyl]-2-carboxy-5,6-dimethylindoline
1-[N-(1,3-Dicarboxypropyl)-L-histidyl]-2-carboxy-4-chloroindoline
1-[N-(1-Ethoxycarbonylhexyl)-L-valyl]-2-carboxy-4-methoxyindoline
1-[N-(1-Ethoxycarbonylheptyl)-L-phenylalanyl]-2-carboxy-6-methyl-indoline
1-[N-(1-Ethoxycarbonyl-3-phenylpropyl)-L-valyl]-2-carboxy-3-hydroxymethyl-5,6-dimethylindoline
1-Carboxy-2-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-valyl]-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonyl-3-methylbutyl-L-histidyl]-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonyl-4-methylpentyl)-L-phenylalanyl]-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1,3-dicarboxypropyl)-L-alanyl]-7,8-dimethyl-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonyl-3-phenylpropyl)isoleucyl]-6-chloro-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonylhexyl)-L-valyl]-6-methoxy-7-methyl-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-histidyl]-6-chloro-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-carboxy-2-phenylthioethyl)-L-alanyl]-7-methyl-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-ethoxycarbonyl-3-p-chlorophenylpropyl)-L-valyl]-7,8-dimethyl-5H-1,2,3,4-tetrahydro-2-benzazepine
1-Carboxy-2-[N-(1-carboxy-2-(3-indolyl)ethyl)-L-valyl]-5H-1,2,3,4-tetrahydro-2-benzazepine
2-(N-1(1-Carboethoxy-3-(4-chlorophenyl)propyl)-L-leucyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
2-(N-1(1-Carboethoxy-3-(3-trifluoromethylphenyl)propyl)-L-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
2-(N-1(1-Carboethoxy-2-(3-methoxyphenyl)ethyl)-L-methionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(4-pyridyl)propyl)-L-alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(4-methoxyphenyl)propyl)-L-lysyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-pyridyl)propyl)-L-leucyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-(1-Carboethoxy-2-(2-thienyl)ethyl)-L-arginyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(methylthio)propyl)-L-isoleucyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-thienyl)propyl)-L-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-phenylethyl)-L-lysyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-(phenoxy)ethyl)-L-lysyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(2-furyl)propyl)-L-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3,4-methylenedioxy-phenyl)propyl)-L-alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-chlorophenyl)propyl)-L-phenylalanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(2-methoxyphenyl)propyl)-L-tyrosyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-(benzofuran-3-yl)ethyl)-L-leucyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(4-methoxyphenyl)propyl)-L-alanyl)-6-chloro-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(phenoxy)propyl)-L-arginyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-(indol-3-yl)ethyl)-L-leucyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(4-methoxyphenyl)propyl)-L-leucyl)-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-pyridyl)propyl)-L-methionyl)-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(methylthio)propyl)-L-leucyl)-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-(4-imidazolyl)ethyl)-L-valyl)-7-methoxy-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-methoxyphenyl)propyl)-L-lysyl)-6,7-methylenedioxy-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-3-(3-chlorophenyl)propyl)-L-histidyl)-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-[N-1(1-Carboethoxy-3-(3-thienyl)propyl)-L-arginyl)-7-methoxy-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

2-(N-1(1-Carboethoxy-2-phenylethyl)-L-tryosyl)-7-chloro-5H-1,2,3,4-tetrahydrobenz[c]azepine-3-carboxylic acid

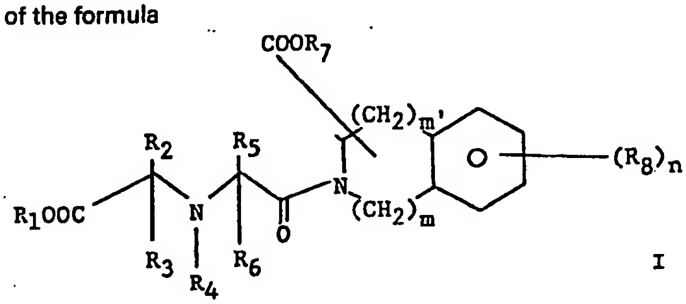
N-(1-Carboxy-2-indanylmethyl)-alanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

The compounds of the present invention have demonstrated potent activity (of the order of I_{50} of 0.02 to 0.20 micromols) in inhibiting the angiotensin converting enzyme (ACEI activity) when tested by the method described in Science *196*, 441—4 (1977). The compounds of the present invention have also demonstrated an I_{50} of about 1 to 2 mg/kg p.o. in inhibiting infused angiotensin I inrats. As such, these would be very useful in the treatment of hypertension.

The compounds may be administered orally or parenterally in the treatment of hypertension, and it will be within the professional judgement and skill of the practitioner to determine the amount to be administered. Suitable dosage forms include tablets, capsules, elixirs and injectables.

Claims

1. A compound of the formula



I

wherein

R_1 and R_7 are hydrogen, lower alkyl or phenyl lower alkyl,

R_2, R_3, R_4, R_5 and R_6 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, fused arylcycloalkyl, aralkyl, cycloalkyl, heterocyclic, substituted lower alkyl, lower alkenyl, and lower alkynyl groups wherein the substituent is hydroxy, alkoxy, halo, amino, alkylamino, mercapto and alkylmercapto groups, and substituted cycloalkyl, aryl and heterocyclic groups in which the substituent is alkyl, hydroxy, alkoxy, hydroxyalkyl, halo, mercapto, alkylmercapto, mercaptoalkyl, haloalkyl, amino, alkylamino, aminoalkyl, nitro, methylenedioxy, and trifluoromethyl;

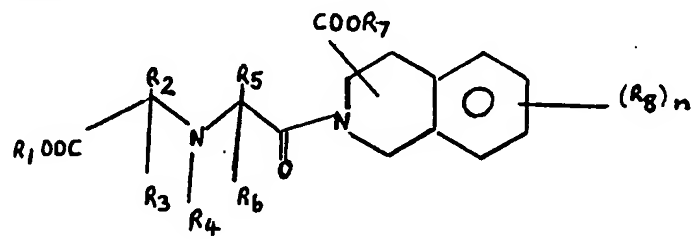
each R_8 is lower alkyl, lower alkenyl, lower alkynyl, nitro, amino, alkylamino, dialkylamino, hydroxy, alkoxy, mercapto, alkylmercapto, hydroxyalkyl, mercaptoalkyl, halogen, haloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, sulfonamido, methylenedioxy, or trifluoromethyl,

m is an integer from 0 to 2 inclusive;

m' is an integer from 1 to 3 inclusive, provided that when m is 0, m' is 2 or 3 and, when m is other than 0, m' is 1 or 2;

n is an integer from 0 to 4 inclusive, and salts thereof, especially pharmaceutically acceptable salts with an acid or a base.

2. A compound of the formula



wherein

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and n are as defined in Claim 1 and salts thereof, especially pharmaceutically acceptable salts with an acid or a base.

3. A compound according to Claim 1 or 2, wherein the $COOR_7$ substituent is attached to a carbon adjacent to the ring nitrogen.

4. A compound according to any of Claims 1—3, wherein R_7 is hydrogen.

5. A compound according to any of Claims 1—4, wherein R_1 is ethyl or hydrogen.

6. A compound according to any of Claims 1—5, wherein R_2 is phenyl-lower alkyl.

7. A compound according to Claim 6, wherein R_2 is phenethyl.

8. A compound according to any of Claims 1—7, wherein R_6 is methyl.

9. A compound according to any of Claims 1—7, wherein R_6 is isopropyl.

10. A compound according to any of Claims 1—7, wherein R_6 is isobutyl.

11. A compound according to any of Claims 1—4, wherein R_2 is phenethyl and R_6 is methyl.

12. A pharmaceutical composition for treatment of high blood pressure which comprises an anti-hypertensively effective amount of a compound according to any of Claims 1—11.

13. The process of preparing a compound of formula I herein which comprises reacting under amide-forming conditions a compound of formula II herein with an acylating derivative of an acid of formula III or formula IV herein;

or reacting a compound of formula VI herein with an α-keto acid or ester of formula VII herein and reducing the resulting imine; or reacting a reacting a compound of formula VI herein with an α-halo acid or ester of formula VIII herein; and

optionally by substitution or conversion reactions introducing various substituents into the said products; and

optionally forming salts thereof, especially pharmaceutically acceptable salts with an acid or a base.

14. A process according to Claim 13, wherein the $COOR_7$ substituent is attached to a carbon adjacent to the ring nitrogen.

15. A process according to any of Claims 13 or 14, wherein R_7 is hydrogen.
16. A process according to any of Claims 13—15, wherein R_1 is ethyl or hydrogen.
17. A process according to any of Claims 13—16, wherein R_2 is phenyl-lower alkyl.
18. A process according to Claim 17, wherein R_2 is phenethyl.
19. A process according to any of Claims 13—18, wherein R_6 is methyl.
20. A process according to any of Claims 13—18, wherein R_6 is isopropyl.
21. A process according to any of Claims 13—18, wherein R_6 is isobutyl.
22. A process according to any of Claims 13—17, wherein R_2 is phenethyl and R_6 is methyl.
23. A pharmaceutical composition according to Claim 12 and substantially as hereinbefore described.
24. A process according to Claim 13 and substantially as hereinbefore described with reference to any of the Examples.

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